

Evaluation of oxidative stress and thyroid hormone status in hemodialysis patients in Gorgan

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ABSTRACT

Aims: The aim of this study focused on serum malondialdehyde (MDA) levels and erythrocyte superoxide dismutase (SOD) and catalase (CAT) activities in hemodialysis patients and compared with control groups. **Materials and Methods:** Forty-five hemodialyzed patients and 45 control groups recruited in this study. Serum creatinine and urea, thyroid hormones (THs) levels and erythrocyte antioxidant enzyme activities were determined. **Results:** Hemodialysis (HD) patients showed higher levels of MDA than control groups ($P < 0.01$), but the levels of thyroxine (T3), free triiodothyronine (fT3), and free thyroxine (fT4), SOD and CAT were low in HD patients ($P < 0.01$). Serum T3, fT3, and fT4 levels were significantly negative correlated with MDA ($P < 0.01$). **Conclusion:** It is concluded that serum lipid peroxidation is markedly increased in HD patients. This means that elevated reactive oxygen species may interact with the lipid molecules in HD patients. HD may cause significant changes in TH levels. Thyroid-stimulating hormone level in HD patients is slightly similar to that of control groups. This suggests that thyroid is able to resynthesize for hormonal urinary losses.

Key words: Antioxidant enzymes, hemodialysis, lipid peroxidation, thyroid hormones

INTRODUCTION

Thyroid hormones (THs) are necessary for metabolic function of the kidneys. The kidney is an organ for metabolism and elimination of THs and a target of some of the iodothyronines' actions. Thyroid dysfunction may effect on glomerular and tubular functions and electrolyte and water (H₂O) homeostasis. It may cause a reduction in glomerular filtration, hyponatremia, and H₂O excretion alteration.^[1-3] Many studies have shown that patients on regular hemodialysis (HD) tolerate a chronic illness which was not involved the thyroid, but these patients indicated low serum thyroxine (T4) and triiodothyronine (T3) levels.^[4,5] Some

studies revealed decreased T3 and T4 levels while the thyroid-stimulating hormone (TSH) levels are not elevated.^[6] There may be an association between THs and the oxidative and antioxidative status in the body. It has been reported that thyroid dysfunction such as hypothyroidism reduces oxidant production which may not protect the organism against oxidant damage.^[7,8] There are limited and controversial studies on the oxidative status of hypothyroidism.^[9-11] Different antioxidant enzymes may protect oxidative effects of free radicals on lipids, proteins, and DNA. These enzymes consist of superoxide dismutase (SOD) and catalase (CAT).^[12] SOD catalyzes the alteration of the superoxide anion into hydrogen peroxide (H₂O₂). H₂O₂ then changed to H₂O by CAT or glutathione peroxidase.^[13,14] Lipid peroxidation which express as malondialdehyde (MDA) may change in different age and ethnic groups, gender and different kinds of diseases.^[15-21] HD is the most effective method in balancing the metabolic

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abnormalities related to renal oxidative stress that causes to morbidity in HD patients.^[22] Chronic renal failure (CRF) patients who are on HD therapy show a high percentage of goiter and thyroid dysfunction and cardiovascular (CV) disorders.^[23-25] Free radicals have been revealed to change the activity of some membrane-bound tissue enzymes.^[26] End-stage renal disease can only be overcome by hemodialysis which can be considered as crucial therapeutic regimens for such kidney diseases and for those subjects which are a candidate for kidney transplantation.^[27] The production of reactive oxygen species (ROS) which are the byproducts of hemodialysis therapy is the main obstacle and complications in hemodialysis application for the end stage renal failure.^[28-30] THs can be altered due to hemodialysis. The THs abnormality may accompany with various disorders, including systemic acidosis, the hemodialysis duration, and endothelial injuries and inflammation.^[31] The aim of this study focused on serum MDA levels which is an indicator of lipid peroxidation and erythrocyte SOD and CAT activities in hemodialysis patients and compared with age-matched control groups in Gorgan.

MATERIALS AND METHODS

Forty-five hemodialyzed patients with mean age 51.88 ± 15.90 years who were referred to the HD unit at 5th Azar Education Hospital of Gorgan Faculty of Medicine, Golestan University of Medical Sciences in Gorgan, Iran in 2015. Patients were compared with 45 age-matched control groups (mean age 48.68 ± 15.60). This study was approved by the Research Deputy Ethics Committee of the Golestan University of Medical Sciences. An informed consent from all subjects had been carried out. HD patients were being treated 3 times a week. Clinical history test was performed from all patients. Patients with diabetes mellitus, liver disease, endocrinal diseases, acute or chronic illness, thyroid disorders and any drug that affect TH were excluded from the study. A 10 ml blood samples were provided after an overnight fast of 12 h. Biochemical tests including serum creatinine and urea, THs (TSH, T3, T4, free triiodothyronine [fT3] and free thyroxine [fT4]) and erythrocyte antioxidant enzymes (SOD [Code number: 706002, Cayman Chemical Commercial Kit, Colorimetric Method, USA] and CAT [Code Number: 707002, Cayman Chemical Commercial Kit, Colorimetric Method, USA]) were determined. The hormonal analysis was done by Monobind Kit (Code Number: 1225-300, Lake Forest CA: 92630, USA) and enzyme immunoassay (ELISA) method. Serum creatinine and urea levels were determined with commercial kits by spectrophotometer techniques (Model JENWAY 6105 UV/VIS) in the Metabolic Disorders Research Center (Gorgan Faculty of Medicine). Serum MDA was determined with Kei Satoh method.^[32] Weight

was measured, while subjects were minimally clothed without shoes, using digital scales. Height was measured in standing position using tape meter while the shoulder was in a normal position. Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Overweight was defined as BMI 25.0–29.9 kg/m² and obese as BMI ≥ 30 kg/m².^[33]

The results are shown as means and standard deviations. SPSS version 16 (SPSS Inc., Chicago, IL, USA) software was used to calculate the statistical analysis. The evaluation of data was done by using independent sample *t*-test and Pearson correlation test. $P < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows clinical and anthropometric characteristics of the HD patients and control groups. There was no difference in serum TSH, age, and BMI among the studied groups. There were well-significant differences in serum T3, T4, fT3 and fT4, MDA, SOD, and CAT compared with control groups. HD patients showed higher levels of MDA than those control groups ($P < 0.01$), but the levels of T3, fT3 and fT4, SOD and CAT were low in HD patients ($P < 0.01$). Table 2 shows relationship between MDA SOD and CAT and THs in HD patients. Spearman correlation analysis showed that the serum T3, fT3, and fT4 levels were significantly negative correlated with MDA [Table 2]. There was no correlation between THs and SOD and CAT.

DISCUSSION

In the present study, we revealed that the thyroid function differed among the HD group compared to the healthy

Table 1: Clinical data of study subjects

Parameters	Healthy subjects	Hemodialysis patients	P
n	45	45	-
Age (years)	48.68±15.6	51.88±15.9	0.330
BMI (kg/m ²)	26.41±2.81	25.92±6.67	0.653
TSH (mIU/mL)	2.13±0.84	2.76±2.21	0.079
T3 (ng/mL)	1.25±0.25	0.83±0.32	0.001
T4 (µg/dL)	7.97±1.17	7.53±2.12	0.222
fT3 (pg/mL)	2.78±0.43	2.51±0.59	0.013
fT4 (ng/dL)	1.35±0.18	0.92±0.31	0.001
Creatinine (mg/dL)	0.91±0.77	10.03±1.92	0.001
Urea (mg/dL)	24.72±2.65	103.86±25.9	0.001
SOD (U/mL)	0.15±0.04	0.08±0.13	0.002
CAT (nmol/min/mL)	16.43±7.04	12.31±6.80	0.001
MDA (nmol/mL)	0.45±1.14	2.98±0.89	0.001

BMI: Body mass index, TSH: Thyroid-stimulating hormone, fT3: Free triiodothyronine, fT4: Free thyroxine, SOD: Superoxide dismutase, CAT: Catalase, MDA: Malondialdehyde, T3: Triiodothyronine, T4: Thyroxine

Table 2: Correlation analyses between oxidative stress biomarkers and thyroid hormones in hemodialysis subjects

Parameters	CAT	SOD	MDA
TSH	$r=-0.016$ $P=0.883$	$r=-0.071$ $P=0.506$	$r=0.037$ $P=0.730$
T3	$r=0.153$ $P=0.150$	$r=0.186$ $P=0.08$	$r=-0.499^*$ $P=0.001$
fT3	$r=-0.145$ $P=0.173$	$r=0.057$ $P=0.593$	$r=-0.321^*$ $P=0.002$
T4	$r=-0.039$ $P=0.716$	$r=-0.167$ $P=0.125$	$r=-0.161$ $P=0.129$
fT4	$r=0.172$ $P=0.104$	$r=0.239$ $P=0.053$	$r=-0.521^*$ $P=0.001$

* $r=-0.499$, $P=0.001$, SOD: Superoxide dismutase, CAT: Catalase, MDA: Malondialdehyde, TSH: Thyroid-stimulating hormone, T3: Triiodothyronine, T4: Thyroxine, fT3: Free triiodothyronine, fT4: Free thyroxine

controls. Serum T3, fT3, and fT4 levels were lower; TSH was slightly higher, and T4 was unchanged among those with HD. Serum lipid peroxidation and antioxidant enzyme activities were significantly high and low among the HD group compared to the healthy controls, respectively. Some studies have shown a low serum level of T3 in patients with end-stage renal disease (ESRD).^[34-41] Lim *et al.*^[35] reported a reduced T3 level and decreased conversion of T4 to T3 in uremic patients.^[35] It is also revealed low serum T4 or fT4 levels in patients undergoing maintenance HD.^[5,36,37,39,40] The serum TSH level in patients with CRF^[34-37,41,42] had been reported to be almost normal. Our study showed that the serum TSH level in the HD patients slightly increased and serum fT3 and fT4 level significantly decreased which is in agreement with other studies.^[5,39,40,43-51] In our study, slightly increase of TSH level in hemodialyzed patients in comparison to control groups was not in accordance with others studies.^[52] The increase in the serum TSH level was not obvious in HD patients. The low serum fT4 and fT3 levels may be responsible for the low metabolism of the body. Studies on a uremic rat model have shown that there may be a difference in the TH metabolism or action in the peripheral system and in the central nervous system in the ESRD patients.^[53,54] Xess *et al.* showed that CRF patients revealed a significant decrease in T3 (in accordance with our study) and T4 (not in accordance with our study) levels in comparison to control groups,^[6,41,55] but serum TSH levels indicated no significant difference in patients and control groups which was in agreement with other findings.^[55] The movement of TH into and out of the extravascular space may be a possible mechanism of TH changes related to HD.^[6] There are different findings on variations in serum lipid peroxidation level and erythrocyte antioxidant enzyme activities due to HD. Some studies indicated an increase while some show a decrease in the levels. In our study, we determined the level of serum MDA of HD patients. MDA uses as a specific and sensitive biomarker for the estimation

of the lipid peroxidation status in different diseases,^[56] including in patients under chronic HD treatment.^[57] Our results show a significant increase of serum MDA in the HD group when compared with the control group. Oxidative damage may depend on different risk factors, but it can be caused by the imbalance between the productions of free radicals and different anti-oxidant enzymes.^[58] Lipid peroxidation disrupts the structural integrity of the lipid bilayer, leading to elevated membrane permeability (the release of hydrolytic enzymes and increasing cell damage) and subsequent impaired electron transport for oxidative phosphorylation in mitochondria and increased lysosomal permeability.^[59] The results of present study indicate that significant difference of anti-oxidant enzyme activities between HD and control group may be related with the loss of antioxidant enzymes, and the reduction of antioxidant enzymes may be related to elevation of lipid peroxidation in hemodialyzed patients which is in agreement with findings of other studies.^[58,60,61] These results show that oxidants and anti-oxidants imbalance may play an important role in the pathogenesis of some diseases. Some findings showed that the elevated MDA level may act as a metabolic signal for kidney damage and protein leakage including THs.^[62] It is reported that there is a significant increase of the blood SOD and CAT activity in plasma and red blood cells of patients undergoing hemodialysis.^[61] Some other studies also indicated that the activity of erythrocyte SOD and CAT increased significantly^[63,64] while another finding showed a decrease of antioxidant enzymes in erythrocyte of CRF patients.^[65-69] Study on hemodialyzed patients showed that significantly lower plasma CAT activity was found.^[65] Study on the animal model kidney of the cytoplasmic SOD has revealed the decrease of the SOD protein abundance in the kidney tissues of the CRF animals which is in accordance with findings that reported the decrease of SOD enzymatic activity in the erythrocytes of patients with CRF^[70-72] and in our results. We found significantly positive correlation between T3, fT3, and fT4 and MDA, which is not in agreement with other studies.^[42] This correlation between MDA and above mentioned TH levels indicate that the alteration of these hormone levels in hemodialyzed patients may depend on variations of lipid peroxidation in these patients. Reduced serum fT3 and T3 may also relate to impaired extrathyroidal changing of T4 to T3. The alteration of T4 and fT4 are less considered in these patients.^[73] The exact mechanisms for the decrease of T3 are not well known, but some studies have shown that the decreased T3 level correlates with poor cardiac prognosis and a strong predictor of death in cardiac patients.^[74] Decreased fT3 is not only important in CRF patients but also in acute and chronic infections; diabetes; and different CV diseases.^[74] Studies have shown that T3 and fT3 are as survival markers in patients with CKD and in

HD patients.^[75] Some researchers have suggested that there is a relationship between T3 levels and thyroid dysfunction and risk of mortality in these patients.^[76]

CONCLUSION

Thyroid dysfunction in HD patients is more common than in general population. HD may influences thyroid function in various ways. Serum lipid peroxidation is markedly increased in HD patients. This means that elevated ROS may interact with the lipid molecules in HD patients. Our results suggest that HD may cause significant changes in TH levels. TSH level in HD patients is slightly similar to that of control groups. This suggests that thyroid is able to re-synthesize for hormonal urinary losses. Because of the high prevalence of thyroid dysfunction in HD patients, it suggests that screening of thyroid function should be needed.

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Conflicts of interest

There are no conflicts of interest.

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